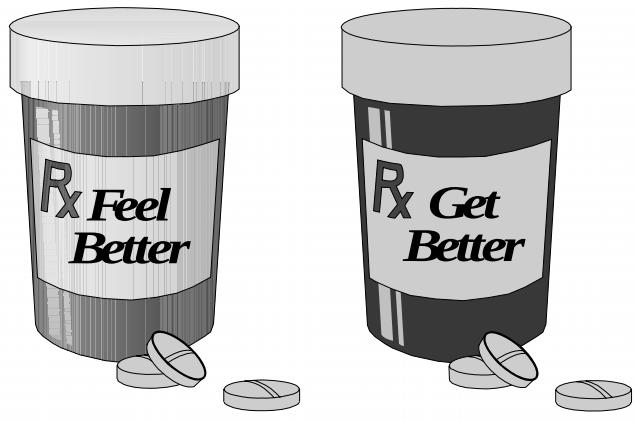
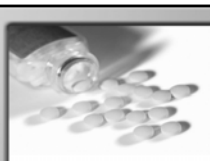
Generic Drugs: Overview of ANDA Review Process

Ted Sherwood
Office of Pharmaceutical Science

Brand vs. Generic



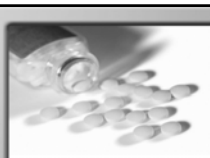
CDER Forum for International Drug Regulatory Authorities



What is the Main Consumer Concern Regarding Generics?

- **Do the quality and performance of generic drugs compare to brand drugs?**

  Often triggered by brand companies and physicians



Legislative History

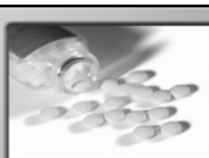
- **1906 Pure Food and Drug Act - establishes regulation of Food and Drugs**
- **1938 Food, Drug and Cosmetic Act - introduced safety standards**
- **1962 Kefauver-Harris Amendments to the FDA&C Act - tightened safety standards and introduced requirement that drugs must be effective**
- ***1984 Hatch-Waxman Act* - created an *abbreviated* mechanism for approval of generic copies of all drugs originally approved after 1962, by stating that pre-clinical and clinical testing did not have to be repeated for generics**

Definition of a Generic Drug

A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use.

When can a Generic Drug be Marketed?

- **After patent & exclusivity protection ends, or**
- **patent owner waives its rights, and**
- **FDA requirements are met**



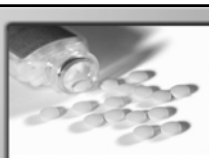
Patent Protection

- **17 years from the date the patent was issued**

or

- **20 years from the date the patent was submitted (to the Patent Office, not FDA)**

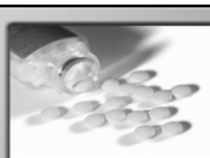
Equates to approximately 12 years of marketing protection.



Patent Filing

- Granted by U.S. Patent and Trademark Office
- Submitted to/for NDAs only
- Covers
  - Drug Substance – Active Ingredient
  - Method of Use – Indication
  - Drug Product – Formulation, Composition
- Published in Orange Book
- Delays final approval date of ANDAs

Approximately 240 patents listed in Orange Book will expire in the next 5 years



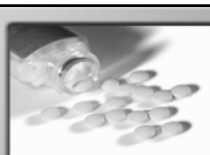
Patent Certification

I Patent Not Submitted to FDA - approval effective after OGD scientific determination

II Patent Expired - approval effective after OGD scientific determination

III Patent Expiration Date (honored) – tentative approval after OGD scientific determination, final approval when patent expires

IV Patent Challenge – tentative approval after OGD science determination, final approval when challenge won



Patent Challenge Process

- Paragraph IV certification by ANDA holder declaring patent invalid, not infringed, or not enforceable
- Notification provision on ANDA holder
- 45-Day clock
  - No lawsuit – challenge successful
  - Lawsuit – 30 months (risk of marketing after meeting FDA approval criteria) or final court decision, whichever earlier

Patent Challenge Successful – Award of 180-Day Exclusivity Period

- Awarded to first ANDA holder to file a complete application with patent challenge
- Protection from other generic competition – blocks approval of subsequent ANDAs
- Protection triggered by:
  - First commercial marketing
  - Forfeiture provisions

Exclusivity

FDA controlled reward primarily to brand name/new drug companies for continued development

CDER Forum for International Drug Regulatory Authorities

Orphan Drug Exclusivity (ODE)

- Orphan drug refers to a product that treats a rare disease - affecting fewer than 200,000 Americans
- 7 years exclusivity
- Granted on approval of designated orphan drug
- OGD works with the Office of Orphan Products

New Chemical Entity (NCE)

- 5 years exclusivity
- Applies to NCEs approved after September 24, 1984

“Other”/Waxman-Hatch

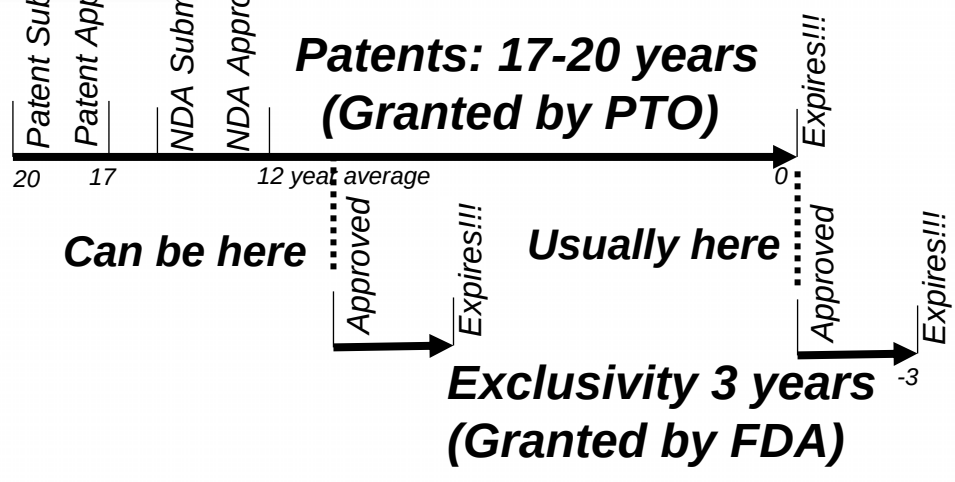
- 3 years exclusivity
- Applies to “significant” approved change where new clinical studies (other than bioavailability studies) were conducted by the NDA holder and were essential for FDA’s approval.
- Changes include new: dosage form, strength, route of administration, indication, dosing regimen, Rx to OTC switch

Pediatric

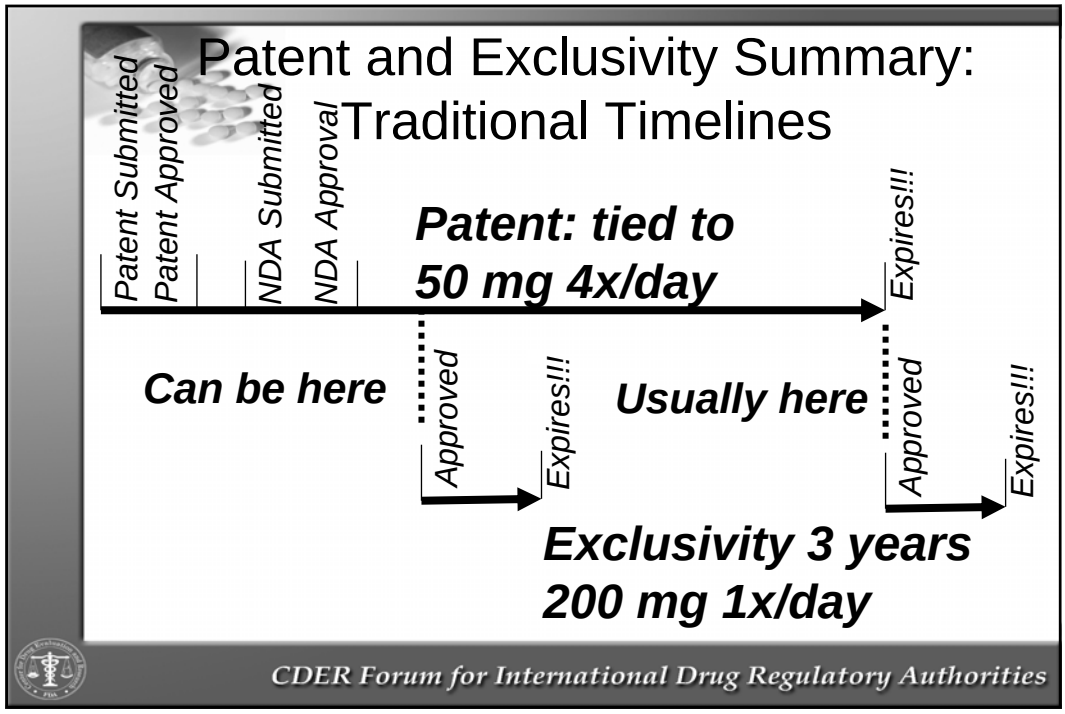
- 6 months of exclusivity
- Additive to patent or other exclusivity protection
- Applies to all applications held by the NDA holder for that active moiety

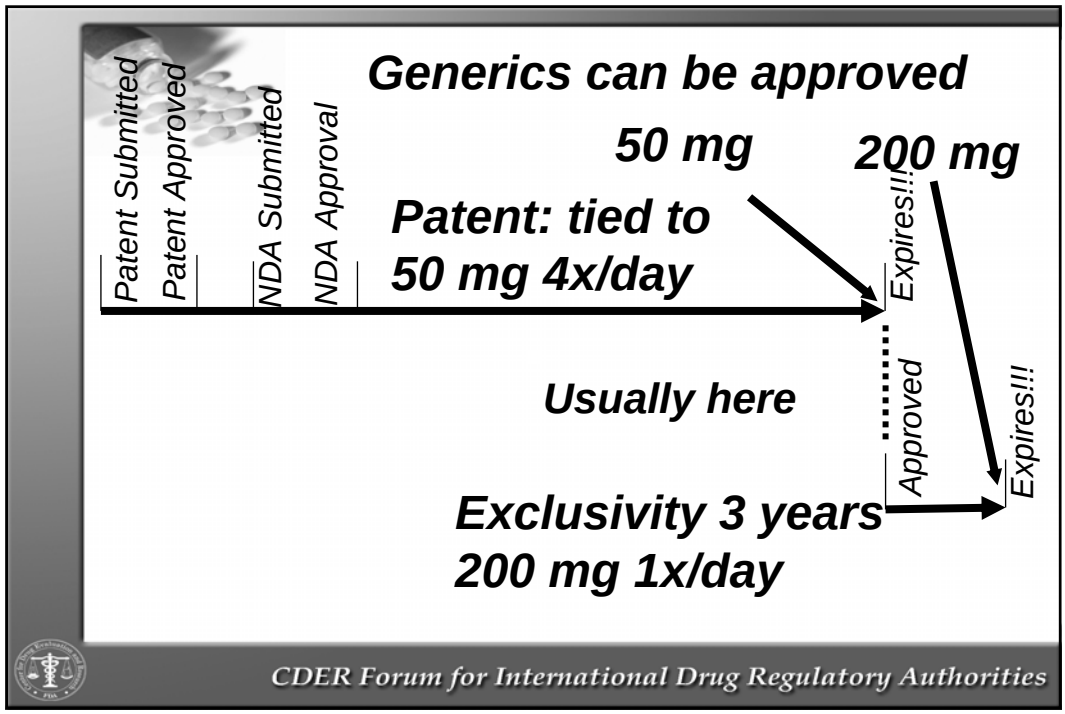
Patent and Exclusivity Questions

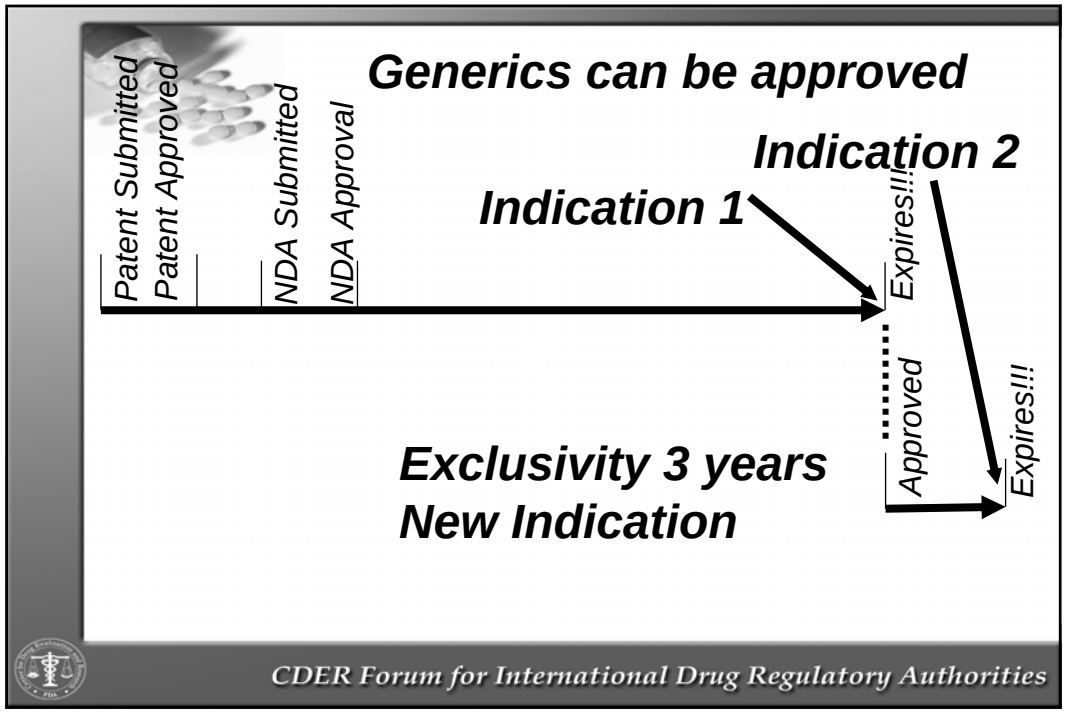
Patent and Exclusivity Summary: Traditional Timelines

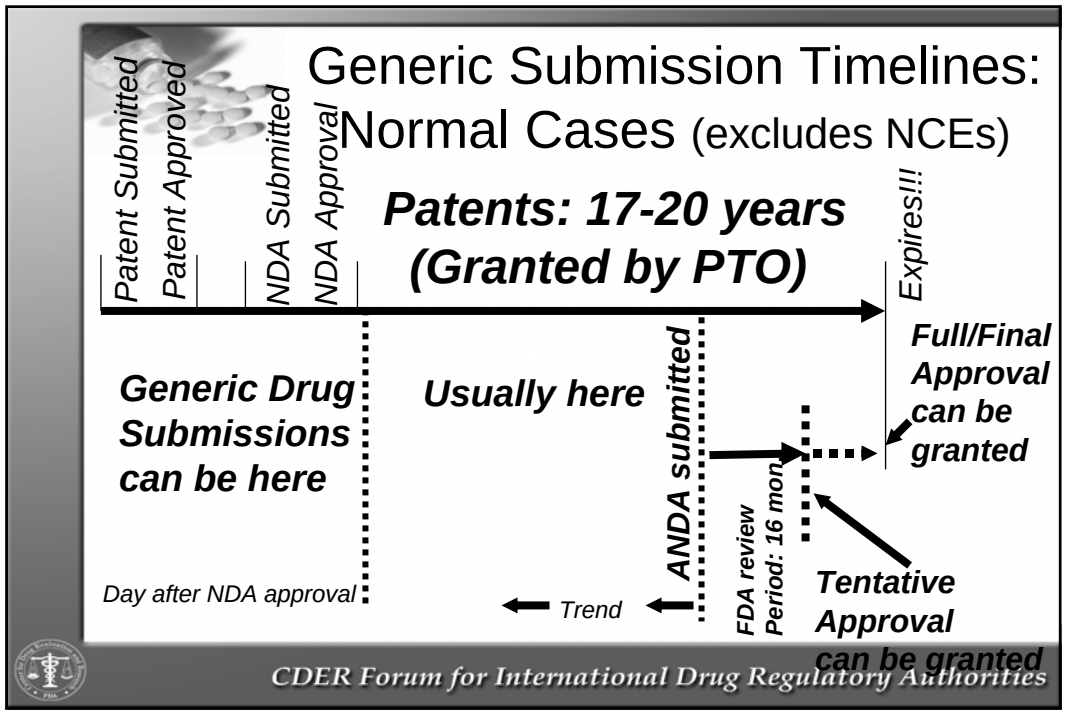


CDER Forum for International Drug Regulatory Authorities


Patent and Exclusivity Summary:
Traditional Timelines
Patent Submitted
Patent Approved
NDA Submitted
NDA Approval
Patent: tied to
50 mg 4x/day
Expires!!!
Can be here
Approved
Expires!!!
Usually here
Approved
Expires!!!
Exclusivity 3 years
200 mg 1x/day
CDER Forum for International Drug Regulatory Authorities


Patent Submitted
Patent Approved
NDA Submitted
NDA Approval
Generics can be approved
50 mg
200 mg
Patent: tied to
50 mg 4x/day
Expires!!!
Usually here
Approved
Expires!!!
Exclusivity 3 years
200 mg 1x/day
CDER Forum for International Drug Regulatory Authorities


Generics can be approved
Patent Submitted
Patent Approved
NDA Submitted
NDA Approval
Indication 2
Indication 1
Expires!!!
Approved
Expires!!!
Exclusivity 3 years
New Indication
CDER Forum for International Drug Regulatory Authorities


Generic Submission Timelines:
Normal Cases (excludes NCEs)
Patent Submitted
Patent Approved
NDA Submitted
NDA Approval
Patents: 17-20 years
(Granted by PTO)
Expires!!!
Full/Final
Approval
can be
granted
Generic Drug
Submissions
can be here
Usually here
ANDA submitted
FDA review
Period: 16 mon
Tentative
Approval
can be granted
Day after NDA approval
Trend
CDER Forum for International Drug Regulatory Authorities

What are the Basic Generic Drug Requirements?

- Same active ingredient(s)
- Same route of administration
- Same dosage form
- Same strength
- Same conditions of use
- Inactive ingredients already approved in a similar NDA

NDA vs. ANDA Review Process

(NDA) Requirements	(ANDA) Requirements
1. Labeling	1. *Labeling*
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies	
10. Clinical Studies	9. Bioequivalence
11. Bioavailability	

CDER Forum for International Drug Regulatory Authorities

Labeling

- "Same" as brand name labeling
- May delete portions of labeling protected by patent or exclusivity (i.e., an indication)
- May differ in excipients and product description (i.e., colors, shapes)

NDA vs. ANDA Review Process

(NDA) Requirements	(ANDA) Requirements
1. Labeling	1. Labeling
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies	
10. Clinical Studies	9. Bioequivalence
11. Bioavailability	

Pharm/Tox

- All inactive ingredients must be approved in either the reference listed drug or similar NDA in same or higher levels. (FDA publishes the ingredient and highest approved levels.)
- Generic focus – is there anything unique to using this ingredient in the proposed generic

NDA vs. ANDA Review Process

(NDA) Requirements	(ANDA) Requirements
1. Labeling	1. Labeling
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. *Chemistry*
4. Manufacturing	4. *Manufacturing*
5. Controls	5. *Controls*
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies	
10. Clinical Studies	9. Bioequivalence
11. Bioavailability	

Chemistry, Manufacturing and Controls (CMC)

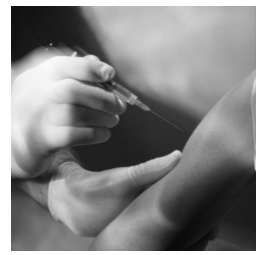
- Components and composition
- Manufacturing and Controls
- Batch formulation and records
- Description of facilities
- Specifications and testing
- Packaging
- Stability

NDA vs. ANDA Review Process

(NDA) Requirements	(ANDA) Requirements
1. Labeling	1. Labeling
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. *Microbiology*
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies	
10. Clinical Studies	9. Bioequivalence
11. Bioavailability	

Microbiology

- Assure the sterility of the product through the manufacturing process – especially important with injectable drug products



NDA vs. ANDA Review Process

(NDA) Requirements	**(ANDA) Requirements**
1. Labeling	1. Labeling
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. *Inspection*
8. Testing	8. *Testing*
9. Animal Studies	
10. Clinical Studies	9. Bioequivalence
11. Bioavailability	

Inspections/Testing

- Assure adherence to and authenticity of data submitted in the application
- Assure manufacturing facilities are in compliance with current good manufacturing practices (CGMPs)
- Assure bioequivalence sites are in compliance with current good clinical practices (CGCPs)
- Conducted primarily by Field/Office of Regulatory Affairs with support from Center (Office of Compliance) and assigned geographically

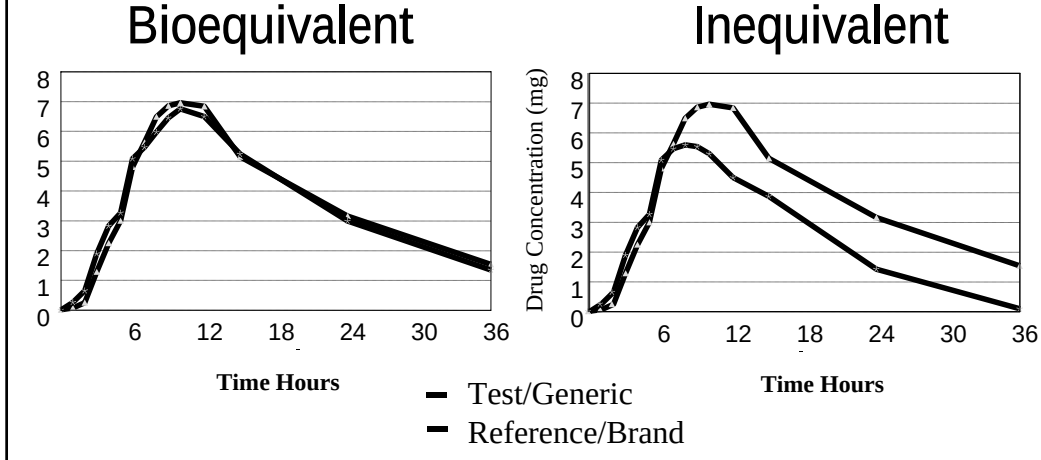
NDA vs. ANDA Review Process

(NDA) Requirements	(ANDA) Requirements
1. Labeling	1. Labeling
2. Pharm/Tox	2. Pharm/Tox
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies	
10. Clinical Studies	9. *Bioequivalence*
11. Bioavailability	

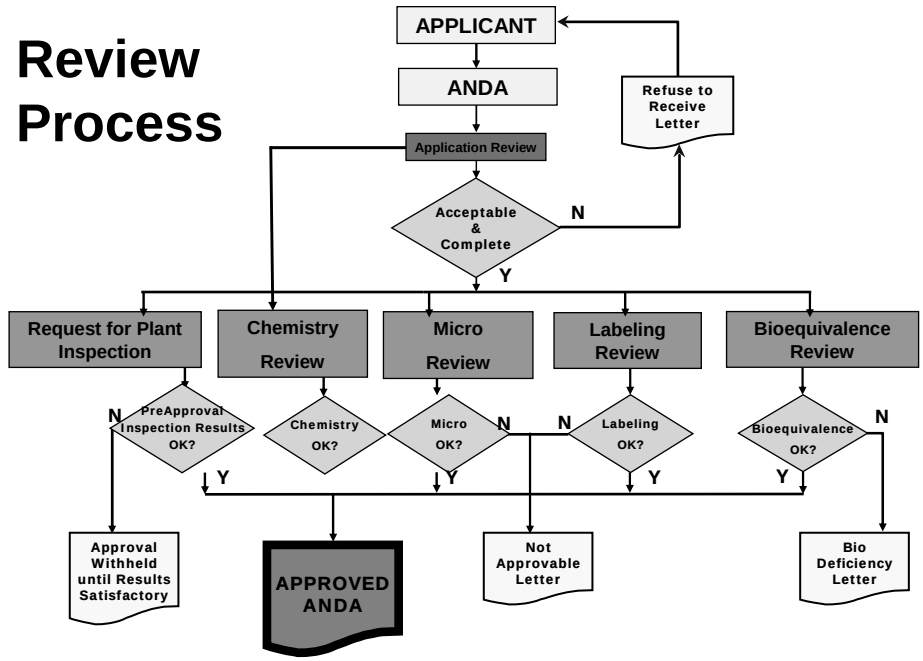
What is Bioequivalence?

A generic drug is considered to be bioequivalent to the brand name drug if:

- **The rate and extent of absorption do *not* show a significant difference from listed drug, or**
- **The extent of absorption does *not* show a significant difference and any difference in rate is intentional or not medically significant**



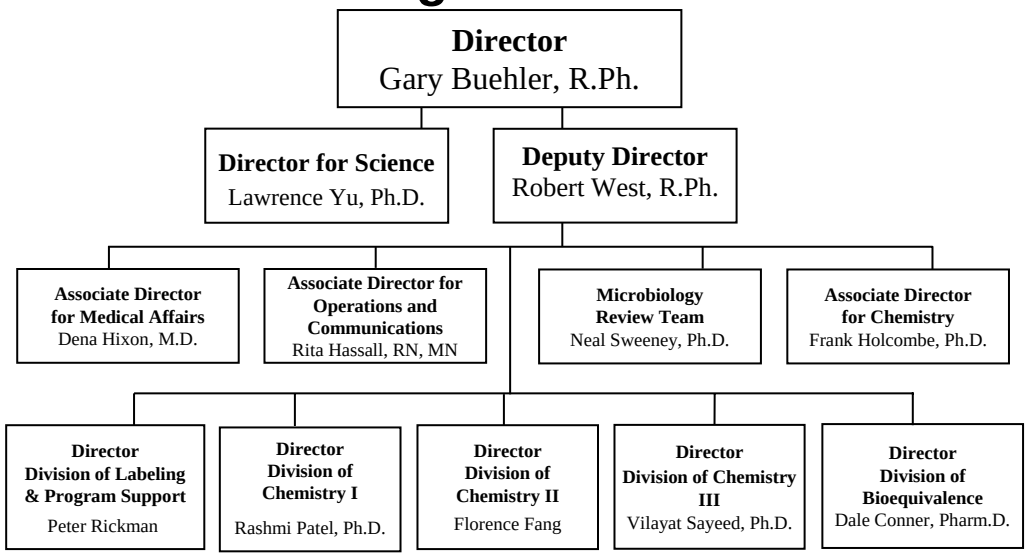
Review Process

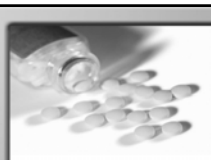


OGD Staff

Total	240
Chemist	105
Bioequivalence/ Pharmacologists	35
Project Managers/ Pharmacists	65
Microbiologists	11
Medical Officers	2
Math Statisticians	2
IT Specialists	3
Admin/Support Staff	17

Organization

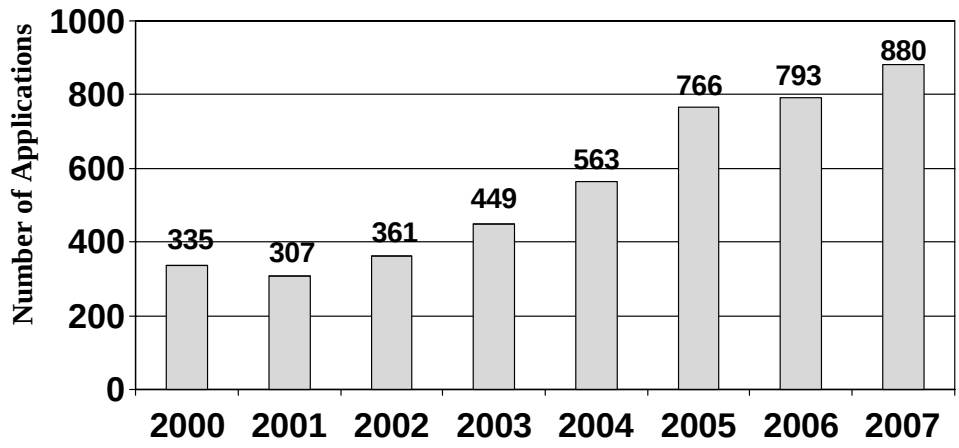




Generic Drug Review Process Issues

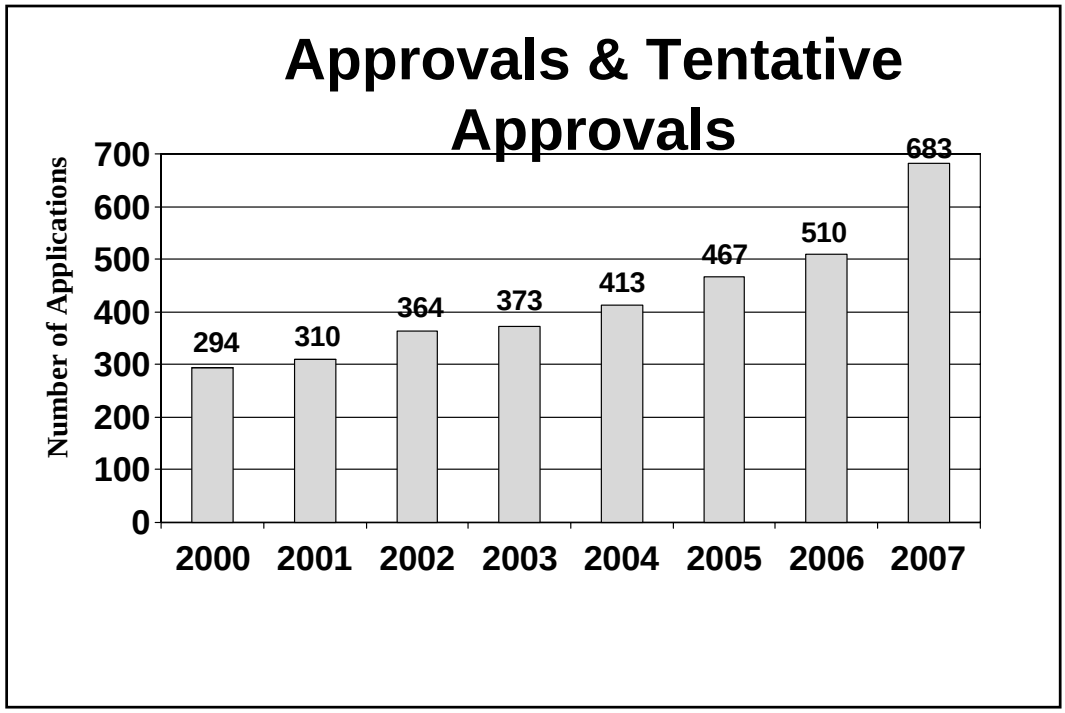
- **Consistency between reviews of multiple applications for the same drug**
- **Fairness in timing of reviews**
- **Patent/exclusivity issues**
- **Demonstration of Bioequivalence**

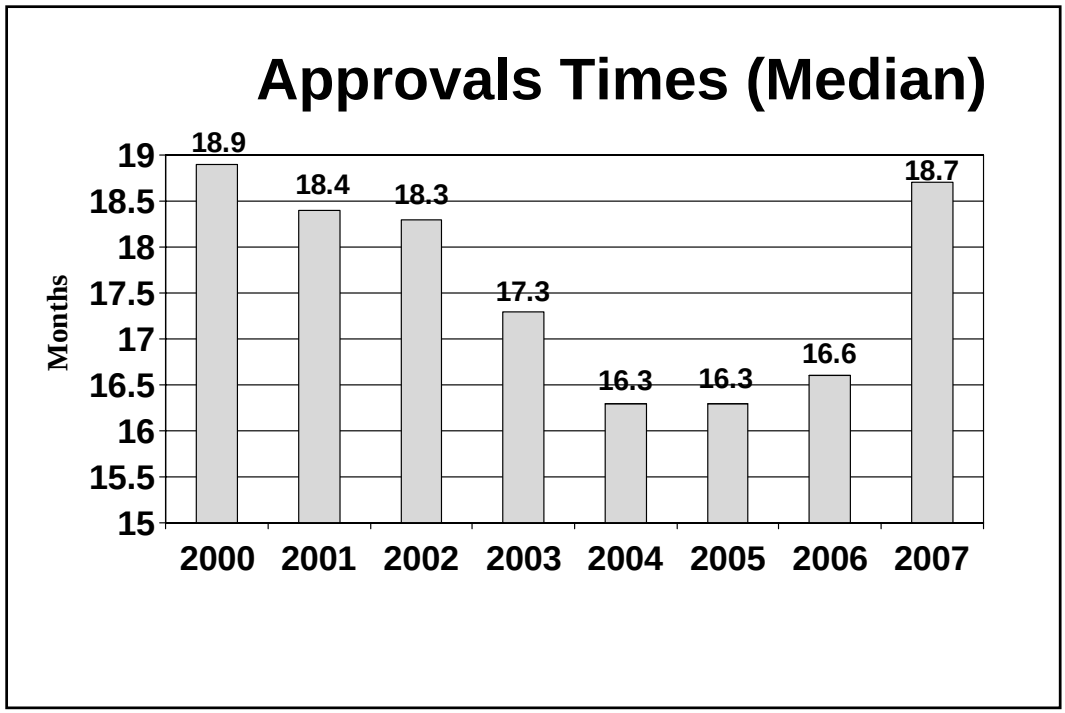
Receipts

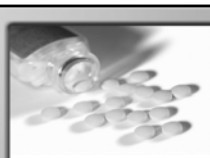


Communications with ANDA Holders

- Acknowledgement of Receipt Letter
  - States date of application filing
- Refuse to Receive (82/year)
- Deficiency Actions (Bio and Labeling)
- Not Approvable Actions (CMC) (944/year)
  - Minor deficiencies – 60-day review clock
  - Major deficiencies – 180-day review clock
- Tentative Approval – approval pending patent expiration/resolution
- Approval – drug product can be marketed

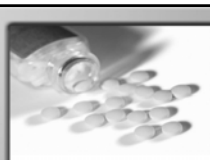

Approvals & Tentative Approvals
Number of Applications
700
600
500
400
300
200
100
0
294
310
364
373
413
467
510
683
2000
2001
2002
2003
2004
2005
2006
2007


Approvals Times (Median)
Months
19
18.5
18
17.5
17
16.5
16
15.5
15
18.9
18.4
18.3
17.3
16.3
16.3
16.6
18.7
2000
2001
2002
2003
2004
2005
2006
2007



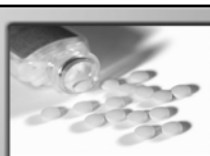
Post Marketing

- Changes to an approved ANDA (21 CFR 314.70)
  - Supplements (3500 received/year)
    - Changes Being Effective (CBE)
    - Changes Being Effective in 30-days (CBE-30)
    - Prior Approval Supplement (PAS)
  - Annual Report (6000 received/year)
    - Summary of product
    - (current) Labeling
    - Distribution data



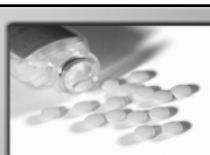
Post Marketing (cont.)

- Reporting of Adverse Drug Events (21 CFR 314.80 and 314.98)
  - 15-Day “Alert Reports” (both serious and unexpected)
  - Periodic Adverse Drug Experience Reports - quarterly for the first three years post-approval and annually thereafter



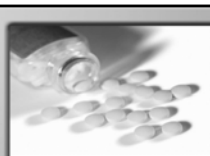
Post Marketing (cont.)

- Manufacturing Compliance Programs
  - Purpose to assure quality of marketed drug products
  - Mechanisms
    - Surveillance
    - Manufacturing/testing plant inspections to assess ANDA holder's continued compliance with good manufacturing practices



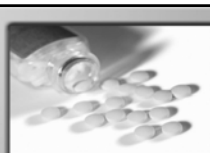
Post Marketing (cont.)

- Therapeutic Inequivalence Action Coordinating Committee
  - Evaluates reports and related information on possible therapeutic failures and toxicity that are attributed to inequivalence for drug products
  - Recommendations regarding appropriate regulatory actions to be taken based on a scientific evaluation and risk assessment



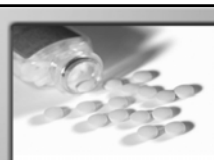
Post Marketing (cont.)

- Promotional Materials – for all brand and generic drug prescription products
- Product quality surveys – a recent review of 1,159 studies submitted to OGD revealed that the average difference between generics and their respective brand drugs was 3%

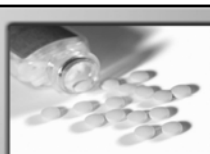


How is Generic Drug Quality Assured?

- First 8 steps of review process identical to NDA process
- Bioequivalence requirements for ANDA's same as NDA's
- FDA has experience with the product
- Product is known to be safe
- Scientific literature published
- Over half are produced by brand name manufactures
- Post-approval product surveys

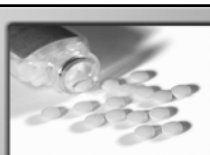


Special Initiatives



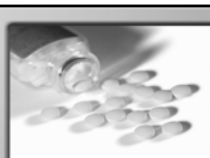
Critical Path Initiative

- Medical product development path is becoming increasingly challenging, inefficient and costly
- Need to update tools used to assess safety and efficacy
- "Toolkit" should contain powerful new scientific and technical methods to improve predictability and efficiency along the critical path from laboratory concept to commercial product



Question Based Review

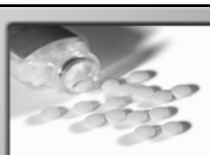
- Keep review up to date with advances in manufacturing and formulation science
  - Quality by Design
  - Process Analytical Technology
- Specifications based on benefit to the consumer – eliminate non-scientific controls with no value to product quality
- Product specific risk assessment
  - Reduce supplements
  - Use FDA resources effectively



Quality by Design

- Understanding the product as it is developed and designed
- Understanding critical attributes
- Designing product and process to be robust with regard to these attributes
- Knowing what happens to those attributes if changes are made in production
- Provide the tools to utilize risk based approaches

CDER Forum for International Drug Regulatory Authorities



Process Analytical Technology

- A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

CDER Forum for International Drug Regulatory Authorities

International Conference on Harmonization (ICH)

- To harmonize the interpretation and application of technical guidelines and requirements
- To reduce or eliminate duplicate testing during research and development in participating countries

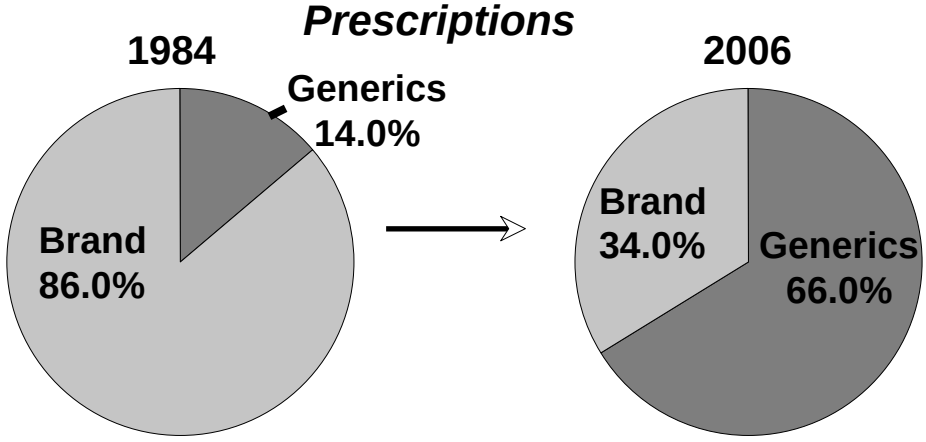
President's Emergency Plan for Acquired Immunodeficiency Syndrome Relief (PEPFAR)

- Standard but expedited ANDA review
- Several ANDAs approved

Economics

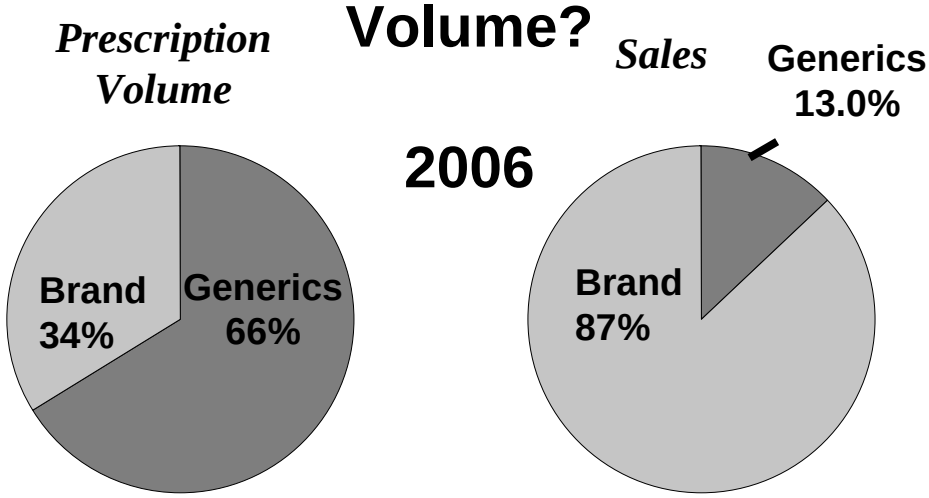
How Frequently are Generic Drugs Used?

Prescriptions



GPhA

Market Share vs. Dollar Volume?



GPhA May 2003 and CNN/Money Aug. 2005

Estimated Savings Through Generic Drug Use

$67 per retail prescription

or

$10.0 Billion a Year

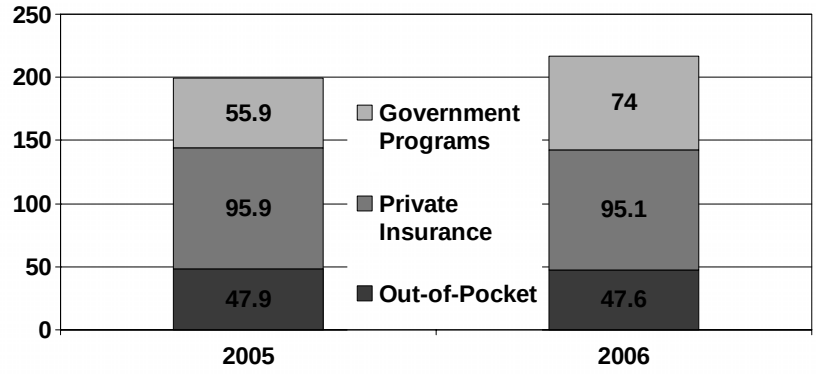
(just in the U.S.)

DHHS Dec. 2004 "if consumers were to buy generic products whenever possible ... we estimate savings to be approximately $17 billion."

GPhA May 2005

Drug Spending

Retail Rx Drugs In Billions

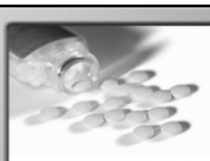


CMS

Typical Price Comparisons

Drug	Generic Price $/30	Brand Price $/30
Lisinopril (Zestril®) 20 mg	20.69	46.69
Citalopram (Celexa®) 20 mg	52.99	100.99
Ciprofloxacin (Cipro®) 500 mg	88.59	215.99
Metformin (Glucophage®) 1000 mg	30.69	71.59
Fluconazole (Diflucan®) 200 mg	372.99	609.99
Fluoxetine (Prozac®) 20 mg	32.29	139.99

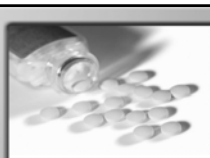
Source: Washington metropolitan area pharmacies, March 2005.



Future

- Over a $50 billion worth of drug products losing protection in the next five years

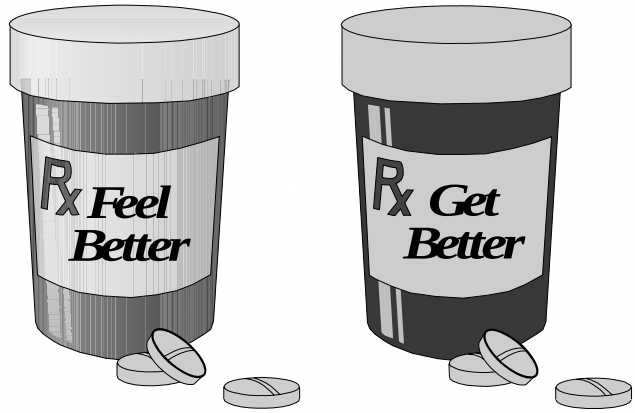
August 3, 2005: 5:52 PM EDT
By Aaron Smith, CNN/Money staff writer



Value of Generics

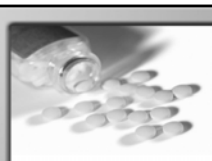
- **Reduce Drug Costs**
- **Increase Drug Use**
- **Prevent Drug Shortages**
  - **Product rationalization**
  - **Supply disruption**

Brand vs. Generic



Summary

CDER Forum for International Drug Regulatory Authorities



APPROVED DRUG PRODUCTS

WITH
THERAPEUTIC EQUIVALENCE EVALUATIONS

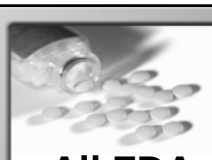
27 TH EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTIONS 505 AND 507 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF MANAGEMENT
DIVISION OF DATABASE MANAGEMENT

2007

CDER Forum for International Drug Regulatory Authorities

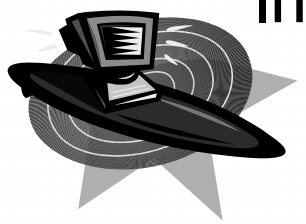


"Orange Book"

- **All FDA approved drug products listed (NDA's, ANDA's and non-monograph OTC's)**
- **Therapeutic equivalence codes: NDAs & ANDAs**
  - **"A" = Substitutable**
  - **"B" = Inequivalent, NOT substitutable**
- **Expiration dates: patent and exclusivity**
- **Reference Listed Drugs - brand drugs identified by FDA for generic companies to compare their proposed products with**

CDER Forum for International Drug Regulatory Authorities

Orange Book Internet Address



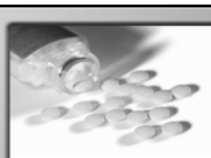
http://www.fda.gov/cder/orange/default.htm

Other Generic Drug Links

- Office of Generic Drugs Home Page:
http://www.fda.gov/cder/ogd/index.htm

- On line training program:
http://www.fda.gov/cder/learn/CDERLearn/genDrugProcess/transcript.htm

CDER Forum for International Drug Regulatory Authorities



Questions:

Ted Sherwood
Special Assistant to the Director
Office of Pharmaceutical Science, CDER
White Oak, Bldg 21, Room 3528
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002
Tel: 301-796-1605, Fax: 301-796-9733
edward.sherwood@fda.hhs.gov